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February 14, 2005

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Citizen Petition – Suitability Petition for Oral Salmon Calcitonin

Dear Sir or Madam:

The undersigned submits this petition pursuant to 21 CFR parts 10.20 and 10.30, as provided for in 21 CFR 314.93, and Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of the Food and Drug Administration to declare that the drug product Oral Salmon Calcitonin, in a dose of approximately 2500 IU or less (to be confirmed by a dose finding study), with 0.25 mg of salmon calcitonin, is suitable for consideration in an Abbreviated New Drug Application (ANDA).

A. Action Requested

Petitioner requests that the Commissioner of the Food and Drug Administration (FDA) declare that Oral Salmon Calcitonin is suitable for submission as an ANDA. The reference-listed drug product upon which this petition is based is Miacalcin® Nasal Spray (calcitonin-salmon) in doses of 200 IU per 0.09 ml activation. Therefore, the petitioner seeks a change in dosage form (from nasal spray to oral tablet or capsule) from that of the listed drug product.

B. Statement of Grounds

1. Basis for Proposed Change

Petitioner submits this petition, in accordance with section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act to request permission to file an ANDA for a new drug in a different dosage form from the reference-listed drug product. FDA must grant this petition unless additional investigations are necessary to demonstrate the safety and effectiveness of the proposed new drug product. The reference listed drug product is a nasal spray containing 200 IU of salmon calcitonin per 0.09 ml activation. The proposed drug product is an oral formulation with the equivalent strength and same active ingredients as the reference listed drug product. This petition seeks FDA's agreement that the change in dosage form (from salmon calcitonin nasal spray to the oral formulation) is suitable for consideration in an ANDA.

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Salmon calcitonin currently is available only in the nasal and injectable forms. Petitioner intends to seek approval of an oral salmon calcitonin product to provide patients with a third alternative dosage form. The oral product is expected to provide more convenient and uniform dosing and to facilitate administration and compliance in the post-menopausal patient population. It will also provide a better alternative for patients who have difficulty administering the currently marketed nasal spray and injections, leading to greater patient acceptance.

FDA has previously approved ANDA suitability petitions allowing for a change in dosage form and Petitioner believes this petition also should be approved. Petitioner does not propose changes in labeling other than those related to the change in dosage form described in this petition. The new product will contain no new chemical entities and all excipients are listed in the U.S. Pharmacopoeia or are Generally Recognized as Safe (GRAS) by FDA. The oral product will have the same indications, is intended for the same patient population, has the same bioavailable dose, and the same recommended use as the marketed product. Therefore, Petitioner expects that there will be no differences in the safety or effectiveness of the new product when used as indicated in the proposed labeling. Draft labeling for the new Oral Salmon Calcitonin product is included as Attachment 1. A copy of the labeling for the reference-listed drug, Miacalcin Nasal Spray, is included as Attachment 2.

2. Determination of Bioequivalence

Salmon calcitonin (in injectable and nasal forms) has been used in the treatment of osteoporosis for more than 30 years. Calcitonin is a hormone that has a direct inhibitory effect on osteoclastic bone resorption through calcitonin receptors on osteoclasts.¹ Salmon calcitonin has been shown to inhibit the bone resorptive process resulting in a decrease in the rate of bone resorption. It has proven effective in the treatment of osteoporosis, which is caused by an excessive rate of bone resorption as compared to bone formation, disrupting the structural integrity of the bone and making it more susceptible to fracture.

C-terminal telopeptide of type I collagen (CTX) is excreted into body fluids when bone tissue is resorbed as a result of osteoclastic activity during bone remodeling. Plasma levels of CTX have been shown to be a sensitive and specific index of bone resorption.² In July 1999, FDA cleared the Serum CrossLaps One Step Elisa kit for the measurement of Type I Collagen C-Telopeptide in human plasma and serum (see Attachment 3) "for *in vitro* diagnostic use as an

¹ Nicholson GC, Moseley JM, Sexton PM, Mendelsohn FA and Martin TJ. "Abundant calcitonin receptors in isolated rat osteoclasts: biochemical and autoradiographic characterization." *J. Clin. Invest.* 178:355-60 (1986).

² Rosenquist C, Fledelius C, Christgau S, Pedersen BJ, Bonde M, Qvist P, et al. "Serum cross-laps one-step ELISA: first application of monoclonal antibodies for measurement in serum of bone-related degradation products from C-terminal telopeptides of type I collagen." *Clin. Chem.* 44:2281-9 (1998); Zikan and Stepan. "Plasma type 1 collagen cross-linked C-telopeptide: a sensitive marker of acute effects of salmon calcitonin on bone resorption." *Clinica Chimica Acta* 316:63-9 (2002).

indicator of human bone resorption . . . [to] be used as an aid in monitoring bone resorption changes of anti-resorptive therapies . . . in postmenopausal women.”³ Zikan and Stepan measured plasma CTX levels to evaluate osteoclastic bone resorption after nasal and subcutaneous administration of salmon calcitonin. Both nasal and subcutaneous salmon calcitonin resulted in a significant (50 to 60 percent) decrease of plasma CTX levels within one hour of administration as compared to baseline, reflecting an inhibition of osteoclastic activity. No significant changes of CTX concentrations were observed during the control period. The authors concluded that plasma CTX is a sensitive marker in detecting acute bone changes following subcutaneous and nasal administration of salmon calcitonin.⁴

Plasma CTX levels have been shown to provide a reliable and sensitive marker of calcitonin activity. Petitioner therefore intends to demonstrate that Oral Salmon Calcitonin, at a dose of approximately 2500 IU or less, to be confirmed in a dose ranging study, is bioequivalent to calcitonin nasal spray based on clinical data comparing the rate and extent of the reduction of plasma CTX levels following the administration of equivalent doses of Oral Salmon Calcitonin and nasal calcitonin. A draft outline of the proposed protocol is included as Attachment 4. In particular, Petitioner proposes to conduct a seven- to fourteen-day randomized, two-way two-arm study of Oral Salmon Calcitonin compared to the nasal calcitonin spray and a carrier placebo. The study will be conducted in a sufficient number of post-menopausal women with confirmed osteoporosis to obtain suitable statistical power. The primary bioequivalence endpoint will be the extent of reduction in plasma CTX levels at appropriate time periods post dosing. As a secondary endpoint, Petitioner also intends to measure serum calcitonin levels; however, blood levels of calcitonin are inherently difficult to measure due its rapid clearance from the bloodstream (approximately 43 minutes) and its biologic fragility which makes it subject to protease action in the bloodstream. Measurement of CTX levels is therefore considered to be a more accurate and reliable measure than calcitonin levels in the blood.

Preliminary clinical data support this approach. In a comparison of oral doses of 1250 IU and 2500 IU of salmon calcitonin and 200 IU Miacalcin Nasal Spray in an open label, sequential study of eight post menopausal females, the oral treatment was well tolerated with evidence of bioavailability and biologic activity. There were significant changes in CTX levels in all treatment arms when compared to baseline and historic controls, although the CTX changes following oral administration of the salmon calcitonin were not directly comparable to the nasal spray due to time variations in the response. The results of the clinical study are summarized in Attachment 5.

3. Pediatric Studies

Petitioner requests a waiver of the requirement to conduct pediatric studies in accordance with FDA regulation 21 CFR 314.55. In support of this request, Petitioner notes that salmon calcitonin is indicated for the treatment of post-menopausal osteoporosis. A full waiver

³ Summary of Safety and Effectiveness (K990843).

⁴ See Zikan and Stepan (2002).

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is appropriate under 21 CFR 314.55(c)(2)(i) because post-menopausal osteoporosis does not afflict a pediatric population and therefore the product will not be used in a substantial number of pediatric patients. The change in dosage form will not change the indication and will not result in use in the pediatric population. The proposed oral calcitonin product is designed to provide a more convenient dosage form for adult patients and would not provide a meaningful benefit over existing therapies for the pediatric patient.

C. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 CFR 25.31.

D. Economic Impact

Petitioner does not believe that an economic impact analysis is applicable in this case, but will agree to provide such an analysis if requested by the agency.

Also, please find in Attachment 6 a certification from John Fitzgerald, Chief Officer, Bone Medical Limited, that complies with the requirements set forth in 21 C.F.R. 10.30.

Please do not hesitate to contact me if you have any questions or comments regarding the contents of this petition.

Sincerely,


John R. Manthei
of LATHAM & WATKINS LLP

Attachments